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Seeing Beyond Retinopathy in Diabetes: Electrophysiological and Psychophysical Abnormalities and Alterations in Vision

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I. Introduction

RETINOPATHY is a common complication of diabetes and is the principal cause of blindness in the adult population. Estimates of the prevalence of retinopathy vary, but the Wisconsin epidemiological study of diabetic retinopathy has documented a higher rate in those with earlier age of onset of insulin-dependent diabetes mellitus (IDDM) that approaches 98% after 15 yr duration (1). Other studies have suggested that eventually up to 75% of all people with diabetes will develop retinopathy of some form (2), and the need for a regular eye examination is a fundamental part of the routine care of all diabetic patients. This usually takes the form of measurement of visual acuity and ophthalmoscopic examination of the lens, anterior chamber of the eye, and the optic fundi through dilated pupils. More refined investigation, such as fluorescein angiography, is usually reserved for assessing the severity of established retinopathy.

Diabetic retinopathy is usually considered to be a disease of retinal blood vessels but is rarely thought of, in a wider sense, as a neurosensory disorder (3). Although abnormalities within the peripheral nervous system are well documented in diabetes, changes within the central nervous system, and particularly their relationship to visual function, have received much less attention. The concept of 'diabetic encephalopathy' was introduced in a case report in 1950 by De Jong (4), who observed diffuse histological abnormalities

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throughout the central nervous system. The significance of these changes proved difficult to investigate as, for many years, electroencephalography (EEG) was the only technique available to study the electrophysiological activity of the brain; however, the information provided by this method is limited, particularly in the assessment of deeper brain structures. In the last two decades, the advent of newer neurophysiological techniques to assess retinal and cerebral function, such as electroretinography and the measurement of brain electrical-evoked potentials, has increased our understanding of normal visual function and the possible effects that diabetes may exert (Table 1). In addition, the development of neuroimaging techniques, including magnetic resonance imaging, has provided evidence for structural changes in the brain associated with diabetes, suggesting that the central nervous system is affected as one of the long-term complications of diabetes (5, 6). If one adds psychophysical tests of visual function, such as contrast sensitivity and hue discrimination, to the above techniques (Table 1) it becomes clear that the examination of visual function provides a case study in integrative neuroscience. In this spirit, the present report surveys aspects of visual function in diabetes and is designed to provide an overview of the subject for the generalist with an interest in diabetes and its complications.

Each of the major electrophysiological and psychophysical methods of assessing visual function has been addressed in the context of diabetes. Given the diversity and scope of these topics, our overview does not attempt to be comprehensive. Each visual process is described in a similar fashion, thereby allowing them to be compared. After an outline of the history and technical aspects of each area, the relevant literature pertaining to its use in the field of diabetes is explored. Particular reference is made to specific aspects of diabetes including type and duration of diabetes, glycemic control, the relationship to age, and retinopathy status. The effect of acute hypoglycemia is also discussed, and, where they are known, anatomical correlations to specific techniques are made.

II. Electroretinography (ERG)

A. Historical and technical aspects

ERG is a special type of evoked potential generating a highly consistent waveform at receptor and postreceptor retinal levels (7). Although first recorded in 1865, this technique was not developed for clinical application until recent years and is generally available only in specialized neurophysiological centers. An active electrode is applied to the cornea with a special contact lens, and the reference electrode is situated on the forehead. The retina is stimulated by a flash of light, and the electrical potential that is elicited is recorded. This technique is able to detect early biochemical and functional abnormalities of the retina before changes are evident with either fluorescein angiography or by direct ophthalmoscopy. Several different types of ERG can be recorded: the conventional flash ERG arises in the receptor and inner layers of the entire retina, and a number of specific waveforms are generated (Fig. 1). Of these, the most commonly reported are 'a' waves (a measure of photoreceptor activity), 'b' waves (corresponding to the inner nuclear layer), and the oscillatory potential (OP) (which reflects changes in the inner retina including the retinal circulation). The pattern ERG (PERG) is the averaged retinal field potential evoked by stimulating the retina with a patterned stimulus such as the reversing checkerboard and is a focal response reflecting ganglion cell activity specifically in the macular area.

Most published work has been performed on patients with disease of the optic nerve, and the relative merits of either flash or PERG are unclear. Some studies have suggested that the PERG can be altered while the flash ERG is unaffected in cases of optic nerve damage (8–10), but contradictory evidence has suggested that PERG has little or no place in the study of optic nerve disease (11, 12).

B. ERG and diabetes

A number of studies have assessed either flash ERG, PERG, or both in patients with diabetes (Table 2). Good

TABLE 1. Functional basis and clinical significance of the tests used to assess vision

Test	Function assessed	Significance
ERG	Measures the electrical potential elicited by the retina in response to a visual stimulus.	Detects early biochemical and functional abnormalities at the retinal level before overt changes are visible.
VEP: P100	Event-related electrical potential generated in the visual cortex in response to a visual stimulus.	Objective measure of function of the visual tracts that cannot be assessed by routine neurosensory examination.
VEP: P300	Event-related brain potential requiring both sensory and cognitive brain function.	Relates to decision making and general cerebral function although its exact functional relevance remains uncertain.
Contrast Sensitivity	Degree of contrast between light and dark required to recognize or detect a visual image.	Measurement of function at different levels of the visual pathway:
Color Vision/Hue Discrimination	Ability to detect and discriminate between different colors of the spectrum.	Macula Visual pathway and cortex Extrastriate visual system Concept of perception

evidence exists that early ERG changes occur in diabetes before the development of retinopathy. Of the studies assessing only flash ERG, the majority report abnormalities, mainly reduced OP amplitude, in diabetic subjects with no evidence of retinopathy compared with nondiabetic controls (13–19). Fewer studies have assessed PERG (20–26), and the results are less conclusive, with some groups reporting abnormalities in the diabetic subjects (20, 24, 25) in contrast to those who found no difference (21–23, 26). Three groups assessed both techniques in the same patient groups (21–23) with variable results. Coupland (23) and Arden *et al.* (21) showed that PERG was unaffected in aretinopathic diabetic subjects despite changes in OP amplitudes. Wanger and Persson (22), however, did not detect any changes in either PERG or OP, concluding that ERG was of limited use in the assessment of early retinal dysfunction in diabetes.

The relative uses of ERG, compared with other electrophysiological tests, have been explored in several studies with contrasting results (20, 27, 28). Uccioli *et al.* (27) examined flash ERG in a group of recently diagnosed patients with IDDM and compared the results with changes in visual evoked potentials (VEPs) (P100; *vide infra*). No significant differences in flash ERG were demonstrated in the diabetic subjects compared with nondiabetic controls, in contrast to a change in P100 latency that was markedly increased in the diabetic group. By contrast, Papakostopoulos *et al.* (28) reported significant changes in 'b' wave amplitude but, although this group also exhibited significant changes in P100 latency, these two variables did not correlate significantly. Martinelli *et al.* (20) demonstrated lower mean PERG results at all spatial frequencies and contrast levels in a group of subjects with IDDM. They also assessed P100 latencies and found that those subjects with reduced PERG amplitude had significantly higher P100 latencies compared with the subjects with normal PERG, leading to the conclusion that change in PERG amplitude is one of the earliest detectable electrophysiological abnormalities of the optic pathway.

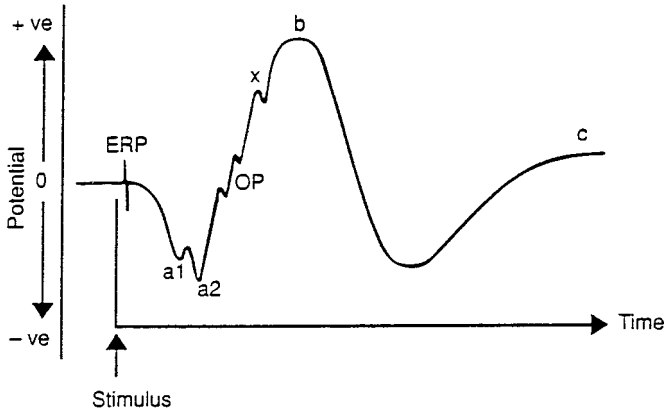

FIG. 1. Diagrammatic representation of the ERG waveform. ERP, Rapid discharge; a, measure of photoreceptor activity (a_1-rods, a_2-cones); b, bipolar cells in inner nuclear layer (most readily recordable component) (b_1-rods, b_2-cones); OP, oscillatory potential (inner retina); c, integrity of pigment epithelium/photoreceptors. [Reprinted with permission from H. Ikeda: In: Halliday AM (ed) *Evoked Potentials in Clinical Testing*. Churchill Livingstone, Edinburgh, 1993, p 118, Figure 3.2 (7).]

C. Type of diabetes

Most ERG studies have examined only subjects with IDDM. There are few data available, therefore, pertaining to the ERG changes in non-insulin-dependent diabetes (NIDDM). Bresnick and Palta (29) included a small number (7 patients) of NIDDM subjects with retinopathy in their study but did not comment on any differences with the larger group of IDDM subjects they also studied (78 patients). Boschi *et al.* (26) observed that PERG amplitudes were lower in their IDDM patients compared with their NIDDM subjects, but no statistical comparison was reported. In their study of pregnant diabetic women, Vingolo *et al.* (30) reported different flash ERG responses, with a greater decrease in b_2/b_1 ratio in the group with NIDDM or gestational diabetes mellitus, compared with IDDM subjects or nondiabetic controls.

D. Duration of diabetes

No flash ERG changes were found in a study of recently diagnosed patients with IDDM (27). Papakostopoulos *et al.* (28), however, detected significantly lower 'b' wave amplitudes in a group of patients with IDDM of less than 6 yr

TABLE 2. Results of ERG studies

Name	ERG changes	Correlation with HbA_{1c}	Correlation with duration of diabetes	Correlation with diabetic retinopathy
Frost-Larsen *et al.* (13) (1983)	↓ OP(NDR)	Φ	Φ	Φ
Wanger and Persson (22) (1985)	NS	Φ	Φ	NS
Arden *et al.* (21) (1986)	↓ PERG(BDR) Variable OP changes	Φ	Φ	↓ PERG(BDR)
Coupland (23) (1987)	↓ OP(NDR/BDR)	Φ	Φ	BDR>NDR (OP)
	↓ PERG(BDR)			↓ PERG(BDR)
Bresnick and Palta (16) (1987)	Delayed OP node	Φ	Φ	PDR>BDR
Bresnick and Palta (17) (1987)	↓ OP	Φ	NS	PDR>BDR
Bresnick and Palta (29) (1987)	↓ OP	Φ	Φ	PDR>BDR
Boschi *et al.* (26) (1989)	NS	Φ	NS	NS
Juen and Kieselbach (15) (1990)	↓ OP(NDR/BDR)	Φ	Φ	NS
Di Leo *et al.* (24) (1990)	↓ PERG(NDR)	Φ	$P = 0.002$	Φ
Caputo *et al.* (25) (1990)	↓ PERG(NDR/BDR)	Φ	$P < 0.05$	BDR>NDR; $P < 0.02$
Lovasik and Spafford (34) (1988)	↓ OP(NDR)	Φ	Φ	Φ
Greco *et al.* (31) (1994)	↓ PERG (children)	NS	NS	Φ
Papakostopoulos *et al.* (28) (1996)	↓ b wave amp (NDR/BDR)	Φ	Φ	BDR>NDR; $P = 0.03$

NS, Not significant; Φ, correlation not performed; NDR, no diabetic retinopathy; BDR, background diabetic retinopathy; PDR, proliferative diabetic retinopathy; OP, oscillatory potential; PERG, pattern electroretinogram.

duration. In five studies the data were specifically analyzed for any correlation between ERG changes and duration of diabetes (17, 24–26, 31). The results are conflicting, as only two groups have reported significant reductions in ERG amplitude with longer duration of diabetes (24, 25).

E. Glycemic control

One study has assessed the effect of short-term strict glycemic control on OP amplitude (13). They reported that OP amplitudes, which were initially abnormal in a group of aretinopathic subjects with IDDM, were normalized after 11 days of strict glycemic control. Greco *et al.* (31), in a study of children with diabetes, found no significant correlation between PERG abnormalities and longer-term glycemic control as assessed by glycated hemoglobin (HbA1c). None of the other studies commented on any relationship between HbA1c and ERG abnormalities, although this association may not have been sought in an era before the Diabetes Control and Complications Trial (DCCT) that emphasized the importance of strict glycemic control in preventing complications associated with diabetes (32).

F. Age of subject

Prepubertal diabetic children have traditionally been considered to be at low risk of developing microvascular complications, including retinopathy (33). The possible existence of early electrophysiological changes affecting the retina, before the development of overt retinopathy, has been investigated by ERG (15, 31, 34). The changes in 'b' wave amplitude demonstrated in adults with IDDM (28) have been observed in adolescents (age range, 12–20 yr) with IDDM, but although both eyes were examined using blue flash ERG, changes were found only in the left eye (34). Mean OP amplitude is also affected in young patients with IDDM (15). Focal ERG was employed to assess the macular function of 20 prepubertal children with IDDM who had no evidence of retinopathy using fluoroscein angiography, and a significant reduction in ERG amplitude was found in either the 2F or 2P component, abnormalities that are thought to correlate with macular neuronal loss. In the diabetic group, 45% exhibited at least one abnormal component of neuroretinal function.

G. Retinopathy status

The association between ERG abnormalities and presence of diabetic retinopathy has been examined in a number of studies (Table 2). Most of the patients studied had evidence of background retinopathy on ophthalmoscopy or fundal photography, although several studies also included patients with proliferative changes (29, 35). The evidence for changes in both PERG and OP amplitude in subjects with background retinopathy is conflicting. Three groups have reported significant changes in PERG amplitude compared with aretinopathic controls (21, 23, 25). These alterations, however, were not found by other investigators (22, 26). Several studies showed significant reductions in OP amplitude in subjects with background retinopathy (23, 28, 29). Perhaps the most compelling evidence for any association is provided by the prospective studies by Bresnick and Palta, which followed a group of young IDDM patients over a period of 15 yr (17, 29). In addition to showing changes in OP amplitude with early retinopathy, they also demonstrated that over time those with initially altered amplitudes were at greater risk of developing proliferative changes (29). Of the subjects who were classified as having 'hypernormal' amplitudes, *i.e.*, greater than normal or normal amplitudes at the start of the study, only 7% and 26%, respectively, went on to develop proliferative retinopathy (PDR) within the next 15 yr. By contrast, over the same time period, 62% with initially reduced amplitudes developed PDR, providing evidence for the predictive potential of such a test. By the end of the study, those with PDR had very low or absent OP amplitudes particularly if the proliferative lesions were central rather than peripheral, a finding that was replicated in another study by Gjötterberg (35). As might be expected, photocoagulation therapy had a further negative effect with a reduction in ERG amplitudes that correlated closely with the number of laser burns, especially those close to the macula (16, 36, 37). No improvement was observed 3 months later (36).

H. ERG and hypoglycemia

The effect of altered blood glucose levels on flash and PERG has been examined in nondiabetic adults (38). Skrandies and Heinrich (38) showed that during hyper- and hypoglycemia, flash ERG amplitudes increased significantly ($P < 0.05$) when compared with the results obtained at euglycemia. By contrast, the PERG results showed a significant *decrease* in amplitude during hyper- and hypoglycemia compared with euglycemia. This difference may be explained by the different retinal structures examined by each test and the possible regional alterations in retinal blood flow that occur with changes in blood glucose outside the normal range.

I. Summary

Changes, both in flash and in PERG, have been demonstrated in adults and children with IDDM, but the relative merits of each test have yet to be established. There appears to be good evidence, however, that ERG abnormalities occur in patients with diabetes before the development of retinopathy. In those with established diabetic retinopathy, the evidence, although not entirely conclusive, is suggestive of further ERG changes that are most apparent in subjects with PDR and laser scarring. ERG has been shown to be of value in assessing those most at risk of developing significant proliferative eye disease in the future and, as such, may have a place in screening patients who require more intensive ophthalmological review.

III. P100 Latency Studies

A. Historical and technical aspects

The P100 response, as part of the VEP waveform, is an averaged event-related brain electrical potential (Fig. 2). It derives its name from the fact that it occurs approximately 100 msec after the stimulus onset and is a highly consistent and reproducible waveform (39–41), which is generated in the striate and parastriate visual cortex in response to a visual

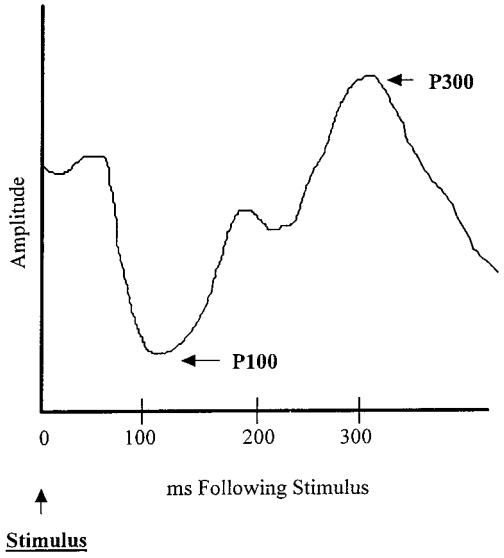

FIG. 2. Visual evoked potential (VEP) waveform

stimulus (Fig. 3). Current methods of clinical assessment using this waveform require the subject to look at a checkerboard. The position of its maximal amplitude is variable, occurring at the inion (the most prominent protuberance on the posterior surface of the skull) in some individuals and corresponding to electrode position Oz in the standard 10–20 electrode placement system. In other subjects the amplitude is greatest in the midline parietal region at the point corresponding to Pz. Therefore, in standard clinical measurement, waveforms are recorded both at Oz and at Pz. The majority of the P100 waveform is generated by the lower half of the visual field and a number of variables will influence the resultant waveform, such as the visual angle subtended by the stimulus and the size of the checks (squares) on the checkerboard. The P100 amplitude is greatest in children during the first decade of life, declining thereafter to remain at a lower level that is stable throughout adult life. A term widely used in the literature is the *latency*, defined as the time interval between the stimulus onset and a specific point (usually the peak) on the waveform, and it has been suggested that the latency increases in people over 60 yr of age (39).

B. P100 and diabetes

A number of studies have examined pattern-stimulated VEPs (P100) in people with diabetes (Table 3). Most studies used pattern-reversal checkerboards as the visual stimulus with variable check sizes and subtended angles, often relying on single-channel recordings of VEP. In many studies no distinction was made between the type or duration of diabetes, the presence of complications, the prevailing visual acuity, or the quality of glycemic control in determining the inclusion of subjects, and the different methodologies employed makes direct comparison between studies difficult, if not impossible.

Most of the studies have demonstrated significant increments in P100 latency in the diabetic subjects compared with nondiabetic controls, although the percentage of patients who had abnormal results varied considerably between

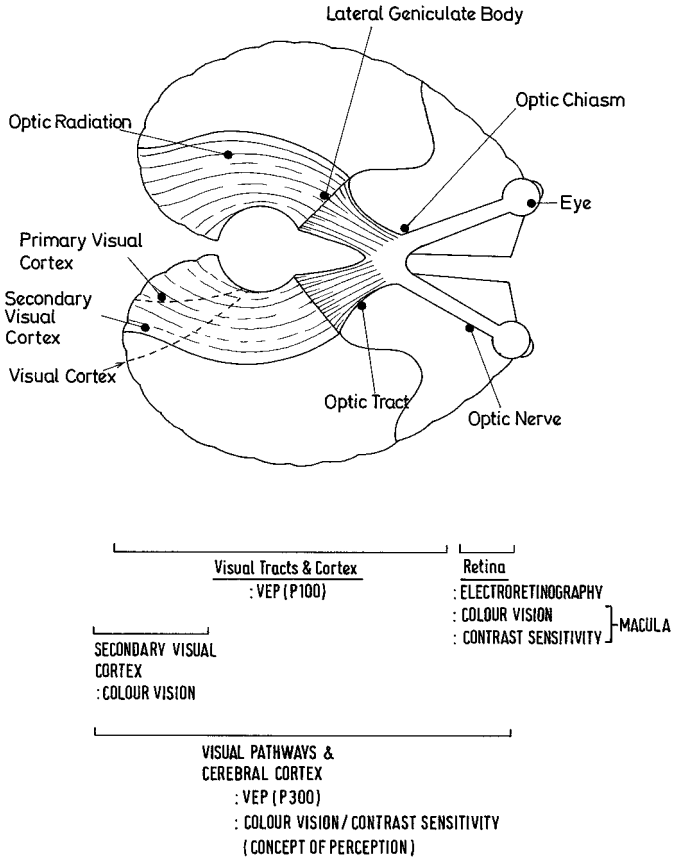

FIG. 3. Schematic representation of anatomical brain correlates to tests of visual function

studies, probably because of differences in study populations and methodologies.

C. Type of diabetes

The type of diabetes is either not specified (42, 43) or, if it is, data on subjects with IDDM and NIDDM have not been analyzed separately (44, 45). Where it is possible to discern the type of diabetes studied, the P100 latencies were increased significantly in IDDM patients by between 9% and 54% (Table 3). Fewer studies have examined the P100 changes in subjects with NIDDM (46–48). Moreo *et al.* (46) reported that 39% of their NIDDM group had P100 latencies more than 2 SD greater than nondiabetic controls. Pozzessere *et al*. (47) directly compared IDDM and NIDDM subjects and found P100 latency changes in a similar proportion of each group (21% in NIDDM and 18% in IDDM). Although the durations of diabetes were equivalent, the NIDDM subjects were older. Algan *et al.* (48) also found no significant difference between subjects with IDDM and NIDDM, demonstrating increased P100 latencies in approximately 28% of each group.

D. Duration of diabetes

Alterations in P100 latencies have been demonstrated within a few weeks of diagnosis of IDDM (27). However, further investigation, including flash ERG and OP, found no

TABLE 3. Demographic details of P100 studies

Name	Type of DM	No.	Age range (yr) (Mean ± SD)	Duration (yr) (Mean ± SD)	Controls (No.)	Incl. Retinopathy	Active electrodes
Puvanendran *et al.* (43) (1983)	Not stated	16	16–71 (Not stated)	3–27 (Not stated)	Yes (35)	No	Single (above inion)
Anastasi *et al.* (50) (1985)	Type 1	50	8–36 (19.8 ± 7.2)	0.08–15 (3.75 ± 4.2)	Yes (36)	No	Not stated
Khardori *et al.* (55) (1986)	Type 1	50	14–63 (34 ± 13)	9–42 (20 ± 9)	Yes (43)	Yes	Not stated
Pozzessere *et al.* (47) (1988)	Types 1 and 2	25	18–32[a] (23 ± 4.7) 41–58[b] (48.9 ± 8.5)	0.6–4 (2.58 ± 1.3)[a] (2.9 ± 1.44)[b]	Yes (40)	No	Single (above inion)
Yaltkaya *et al.* (42) (1988)	Not stated	25	12–78 (50.6)	1–15 (6)	Yes (30)	No	Single (above inion)
Algan *et al.* (48) (1989)	Types 1 and 2	50	Not stated (39.8 ± 14.8)	Not stated (10.4 ± 8.3)	Yes (54)	Yes	Single (Oz)
Mariani *et al.* (45) (1990)	Types 1 and 2	35	37–60 (52 ± 6.4)	1–33 (10.7 ± 8.8)	Yes (35)	No	3 (Oz, O1, O2)
Martinelli *et al.* (20) (1991)	Type 1	35	10–27 (17.2)	4.5–17 (8.7)	Yes (20)	No	3 (Oz, Cz, Fpz)
Pozzessere *et al.* (56) (1991)	Type 1	16	20–64 (33.2 ± 12.6)	1–27 (9 ± 7.7)	Yes (16)	Not Stated	3 (Fz, Cz, Pz)
Ziegler *et al.* (44) (1994)	Types 1 and 2	12	22–50 (38.3)	0.1–15 (5.9)	Yes (12)	Yes	Single (Oz)
Ziegler *et al.* (49) (1994)	Type 1	21	Not stated	Not stated	Yes (12)	Yes	Single (Cz)
Moreo *et al.* (46) (1995)	Type 2	18	Not stated (51.1 ± 6)	1–23 (7.9 ± 5.3)	Yes (35)	No	3 (Oz, O1, O2)
Uccioli *et al.* (27) (1995)	Type 1	10	25.2 ± 6.78	0.44 ± 0.29	Yes (10)	No	Single (Oz)
Papakostopoulos *et al.* (28) (1996)	Type 1	56	16–54 (30.9 ± 9.7)[c] (33.9 ± 12.1)[d]	Not Stated	Yes (24)	Yes	5 (Oz and Lateral 4)
Cirillo *et al.* (53) (1984)	Type 1 (children)	30	7–22 (14.3 ± 3.8)	1–12 (5.6 ± 4.7)	Yes (28)	Yes	Single (above inion)
Comi *et al.* (54) (1987)	Type 1 (children)	71	9–21 (15 ± 3)	5–17 (8.6 ± 3)	Yes (33)	Yes	Single (Oz)
Lovasik and Kergoat (14) (1993)	Type 1 (children)	30	12–20 (Not stated)	Not stated (5.6 ± 4.6)	Yes (30)	No	Single (above inion)

[a] IDDM.
[b] NIDDM.
[c] Subgroup with no retinopathy.
[d] Subgroup with retinopathy.

differences compared with nondiabetic controls, suggesting that the abnormalities were functional rather than structural and related to the metabolic disturbance in the absence of pathological changes in the retina. This theory is supported by a separate study (44) assessing the effects of improving glycemic control on P100 latency (*vide infra*). By contrast, Ziegler *et al.* (49) did not detect any changes in either P100 latencies or brainstem auditory evoked potentials (BAEP) in newly diagnosed IDDM patients, nor did they find any alterations in P100 in those with IDDM of longer duration, with or without peripheral neuropathy, which is at variance with other published data (Table 3). Prolonged P100 latencies have been found within 4 yr of diagnosis in patients with IDDM and NIDDM (47) and, in a different study, within 6 yr of the onset of IDDM (28).

The evidence for an association between duration of diabetes and VEP abnormalities is limited, in keeping with the presence of P100 abnormalities in people with recently diagnosed diabetes. Of the 10 studies that have specifically examined this association, a significant positive correlation with the duration of diabetes was described in only three reports (42, 45, 50) (Table 3). However, several studies are prone to type 2 statistical error, because of the small number of subjects studied.

E. Glycemic control

Improving glycemic control has been shown to alleviate the symptoms of peripheral neuropathy (51). Measurement of VEPs (P100) in a group of poorly controlled patients (including IDDM and NIDDM) showed that, after 3 days of near-normoglycemia achieved by continuous subcutaneous insulin infusion, a significant shortening of P100 latencies had occurred, although these still remained significantly prolonged in comparison with nondiabetic values (44). In view of the rapid rate of improvement, the authors proposed that the changes in P100 latency resulted from metabolic effects. By contrast, short-term hyperglycemia (of <3 h duration) does not significantly affect monocular VEPs in IDDM subjects, irrespective of the duration of diabetes or the presence of diabetic retinopathy (52). Many of the studies sought a correlation between longer term glycemic control (estimated by glycated hemoglobin) and P100 latency alterations. The evidence for an association with glycemic control (Table 4) is

TABLE 4. Results of P100 studies

Name	P100 changes	Correlation with HbA_{1c}	Correlation with duration of diabetes	Correlation with peripheral nerve conduction
Puvanendran *et al.* (43) (1983)	81% ↑ latency	NS	NS	Positive correlation (median nerve)
Anastasi *et al.* (50) (1985)	30% ↑ latency	NS	$r = 0.36$	Φ
Khardori *et al.* (55) (1986)	9% ↑ latency	$P > 0.05$ (NS)	$P > 0.05$ (NS)	Φ
Pozzessere *et al.* (47) (1988)	18.2% ↑ latency[a] 21.4% ↑ latency[b]	$r = -0.312$ (NS)	Φ	Φ
Yaltkaya *et al.* (42) (1988)	72% ↑ latency	Φ	$r = 0.64$	$P < 0.001$ (sural nerve)
Algan *et al.* (48) (1989)	28% ↑ latency	NS	NS	Φ
Mariani *et al.* (45) (1990)	42.8% ↑ latency[c]	$r = 0.38$ ($P < 0.005$)	$r = 0.38$ ($P < 0.005$)	$r = 0.48$ ($P < 0.01$)
Martinelli *et al.* (20) (1991)	54% ↑ latency	NS	NS	Φ
Pozzessere *et al.* (56) (1991)	↑ latency	NS	NS	Φ
Ziegler *et al.* (44) (1994)	33% ↑ latency	NS	NS	Φ
Ziegler *et al.* (49) (1994)	NS	Φ	Φ	Φ
Moreo *et al.* (46) (1995)	38.8% ↑ latency	NS	NS	Φ
Uccioli *et al.* (27) (1995)	↑ latency	Φ	Φ	Φ
Papakostopoulos *et al.* (28) (1996)	↑ latency	Φ	Φ	Φ

NS, Not significant; Φ, correlation not performed.
[a] IDDM.
[b] NIDDM.
[c] Peripheral neuropathy group only.

less compelling than that for duration of diabetes, with only 1 (45) of the 10 studies demonstrating a significant correlation, and that study had examined patients with NIDDM.

F. Age of subject

Several studies have assessed VEPs (P100) in children and adolescents with IDDM, the majority of whom had no overt retinopathic changes. Two studies reported significantly prolonged P100 latencies [30% (53) and 27% (54)] both in the pre- and the postpubertal diabetic children, which are comparable in magnitude to the results observed in adults with IDDM (Table 3). No association was identified either with duration of IDDM or with glycemic control. However, in a different study (34), no changes in P100 latency were observed in a cohort of young subjects with IDDM.

G. Retinopathy status

Some of the study cohorts included patients who had evidence of diabetic retinopathy on ophthalmological assessment (28, 44, 48, 49, 55) (Table 3). In three studies (28, 48, 55) no significant correlation was identified between P100 changes and the presence of retinopathy. In a further study, no significant changes in P100 latency were identified for any of the groups (49). Possible associations with other diabetic complications, including nephropathy and peripheral or autonomic neuropathy, failed to achieve significance in two studies (48, 55).

H. Peripheral neuropathy

The evidence for an association between changes in peripheral and central neurophysiological function is conflicting. Two studies have reported positive correlations between abnormalities in peripheral nerve conduction and changes in P100 latency (43, 45). By contrast, Yaltkaya *et al.* (42) did not find a significant correlation with sural nerve conduction velocity. Ziegler *et al.* (49) assessed cerebral glucose metabolism in addition to multimodal evoked potentials (including P100, P300, BAEP, and peripheral nerve conduction velocities) and, although no significant P100 changes were found, cerebral glucose metabolism was significantly lower in the neuropathic group, suggesting a possible association between peripheral diabetic neuropathy and cerebral glucose consumption. Pozzessere *et al.* (47) identified significant abnormalities both in peripheral and central nerve conduction in IDDM and NIDDM subjects, but no correlations between these phenomena were performed. The association between short-latency evoked potentials (visual P100, BAEP, and somatosensory evoked potentials) and auditory P300 (a cognitive rather than sensory event-related potential) was investigated in IDDM subjects (56). Although both latencies were increased significantly in the diabetic group, no significant correlation was observed between the two parameters.

I. P100 and hypoglycemia

Many of the visual function parameters that were discussed above with respect to diabetes *per se* have also been examined during acute hypoglycemia. Several studies have shown no change in corrected visual acuity during acute hypoglycemia (57, 58) despite a fall in intraocular pressure (59) and a reduction in volume and depth of the anterior chamber of the eye (60). Measurement of VEPs during acute hypoglycemia (venous blood glucose levels below 2.5 mmol/liter) has demonstrated prolongation of the P100 latency, which did not differ significantly between diabetic and nondiabetic subjects (57). This conflicts with the results of another study, which failed to show any effect of moderate hypoglycemia (venous blood glucose 2.4 mmol/liter) on VEP latency in nondiabetic subjects (61). Concurrent EEG changes were observed in both studies (57, 61) with an increase in slow waves (δ- and θ-bands) at the expense of fast α-waves, particularly in the frontal regions of the brain. This finding was replicated by Tallroth *et al.* (62) but not by Lindgren *et*

al. (63) in their respective studies of the effects of acute hypoglycemia in nondiabetic subjects. [It is of interest that acute hypoxia provokes similar frontal lobe changes in patients with epilepsy (64)]. The EEG changes recovered more rapidly than those associated with the VEPs, with rapid normalization after resolution of the hypoglycemia. These EEG findings suggest that the frontal lobes are more sensitive to acute hypoglycemia than other parts of the brain; this supposition is supported by neurophysiological, cognitive, and histological studies (65–68). However, a case report of temporary acute cortical blindness (69), induced by hypoglycemia in a child with Von Gierke's syndrome, suggests an alternative explanation of localized cerebral anoxia induced by hypoglycemia (which alters regional cerebral blood flow), implying that the occipital cortex may also be vulnerable. In a separate report, Gold and Marshall (70) describe a case of cortical blindness and cerebral infarction occurring as a result of a severe episode of hypoglycemia.

Kern *et al.* (71) investigated the effect of human *vs.* porcine insulin on sensory processing by assessing VEPs (P100) during euglycemia and hypoglycemia in a double-blind crossover study in nondiabetic subjects. This showed reduced amplitude and increased latency of the VEP components during hypoglycemia, which were significantly stronger with porcine insulin compared with human insulin, suggesting a direct modulation of visual processing during hypoglycemia that was affected by the species of insulin.

J. Summary

In conclusion, good evidence exists for abnormalities occurring in the P100 response in people with diabetes before the development of overt retinopathy, ranging from the newly diagnosed patient with IDDM to those with diabetes of long duration. Short-term improvements in blood glucose may normalize the P100 latency. The correlations between retinopathy, P100, glycemic control, and duration of diabetes are generally nonsignificant. Although this diminishes the value of the test in diabetes, the measurement of P100 has been shown to be an important specialized diagnostic tool in assessing the neural pathways relating to visual function. There is some evidence to suggest that P100 latency is prolonged during acute hypoglycemia in diabetic subjects, but the findings from different studies are conflicting and no significant difference between P100 latency changes during hypoglycemia in diabetic and nondiabetic subjects has been demonstrated.

IV. P300 Studies

A. Historical and technical aspects

The P300 wave is a component of the averaged electrical brain potential elicited under certain evoking conditions. It was first reported in the 1960s (72) and was initially described as a late positive component evoked by meaningful stimuli, only occurring when the subject paid attention to the task (73). The P300, or P3 as it is also known, derives its name from the fact that its peak latency occurs approximately 300 msec after the stimulus onset in young adult subjects. Like the P100 waveform, amplitude and latency can be measured, but it differs from P100 in that it is an event-related potential requiring mental activity on the part of the subject and is often termed a cognitive or endogenous potential (74). P300 is generally evoked by 'oddball' tasks in which the subject is presented with a stimulus train containing two different stimuli (visual or auditory) in random order, one occurring much more frequently than the other. The subject is asked to concentrate on counting the infrequent stimuli. Whereas both the frequent and rare stimuli evoke a positive potential at about 200 msec post-stimulus (P200 or P2), only the rare, attended-to stimulus evokes a P300 response. The P300 waveform is maximal in the centro-parietal region, is known to correlate with performance on psychometric tests of ability, and is related to decision making (74). The wave can be separated into two components, the earlier one corresponding to a frontal distribution in the brain and the later one to the parietal area. The mechanism of its generation is largely unknown but is thought to be related to stimulus evaluation and may be occurring in multiple locations within the brain simultaneously. P300 amplitude varies with the improbability of the target, possibly reflecting resource allocation processes, while latency alters with the difficulty of discriminating the target stimulus from the standard and reflects stimulus evaluation time (73). P300 latency can be affected by a number of coexisting metabolic or psychological conditions such as hypoglycemia, alcoholism, psychotic illness, and dementia, and it increases with age in nondiabetic individuals (74).

B. P300 and diabetes

In contrast with the numerous studies examining P100 latencies in people with diabetes, relatively few similar studies exist that have investigated the effect of diabetes on visual P300 latency. Some investigators have used P300 generated by an auditory stimulus and studied the association with hypoglycemia, peripheral nerve conduction velocities, or cerebral glucose metabolism (49, 56, 62, 75). Only four studies (63, 76–78) have used visual P300 waveforms generated by a checkerboard stimulus and have examined the specific effects in diabetic (77, 78) and nondiabetic (63, 76) subjects during conditions of euglycemia (76–78) and hypoglycemia (63, 76, 77).

C. Type of diabetes

Mooradian *et al.* (78) studied 43 people with NIDDM and compared their P300 characteristics with 41 age-matched nondiabetic controls. It is not apparent whether the subjects were matched on grounds of cognitive ability, a variable known to affect P300 latency (79). P100 and P300 latencies were elicited using a checkerboard as visual stimulus, and, in addition, an EEG and a number of psychological tests of cognitive function and memory were performed. Recordings were made at Fz, Cz, and Pz electrode placements, and no significant differences were detected between the two groups for either the P100 or the P300 latencies. The authors indicated that their electrode placement was designed specifically to measure P300 latency; the P100 latency was derived

indirectly. A trend was observed for longer P300 latencies at both Fz and Cz in the diabetic group but did not achieve statistical significance. The induction of transient hyperglycemia in the nondiabetic group by an intravenous infusion of dextrose did not significantly alter the P300 latency. A single study has examined visual P300 parameters in patients with IDDM (77). The baseline P300 results did not differ significantly from the age-matched nondiabetic controls in the IDDM group in whom glycemic control was poor.

D. Glycemic control and duration of diabetes

Although no data are available pertaining to the relationship between visual P300 latency and either duration of diabetes or level of glycemic control, the studies investigating auditory P300 have not demonstrated any association with either duration of diabetes or glycated hemoglobin (49, 56).

E. Retinopathy status

No studies have been done examining the effect of diabetic retinopathy on visual P300 amplitude or latency.

F. P300 and hypoglycemia

Acute hypoglycemia has been shown to affect visual P300 waveforms significantly in several studies (63, 76, 77). In nondiabetic subjects, lowering the arterialized blood glucose to 2.6 mmol/liter significantly increased the P300 latency, with full recovery occurring within 45–75 min after normoglycemia was restored (76). In a similar study, Lindgren *et al.* (63) demonstrated that hypoglycemia (arterialized blood glucose of 2.5 mmol/liter) maintained for 1 h, significantly reduced the visual P300 amplitude during complex tasks, and recovery was not complete until 40 min after restoration of normoglycemia. Blackman *et al.* (77) also assessed visual P300 during hypoglycemia in IDDM patients. Baseline P300 values did not differ from nondiabetic controls, but when the arterialized blood glucose was lowered to 2.5 mmol/liter, latencies increased significantly in the diabetic group and eventually returned to normal after normoglycemia was restored.

Evidence regarding the relationship between changes in visual and auditory P300 latencies during acute hypoglycemia is conflicting. Auditory P300 is a simpler test to administer, and a number of studies have measured this during hypoglycemia (62, 75), showing an increased latency in nondiabetic subjects and reduced amplitude both in diabetic and nondiabetic individuals at arterialized blood glucose concentrations below 3.0 mmol/liter (75) and between 1.6–2.3 mmol/liter (62). In one study (75) these changes were correlated with BAEPs and were preceded by the secretion of counterregulatory hormones. Several studies have compared visual and auditory P300 responses during acute hypoglycemia, and conflicting results have been reported (63, 76). Blackman *et al.* (76) observed increments of a similar magnitude both in auditory and visual P300 latencies at an arterialized blood glucose of 2.6 mmol/liter, whereas Lindgren *et al.* (63) failed to demonstrate any alterations in either auditory P300 latency or amplitude during moderate hypoglycemia (arterialized blood glucose 2.5 mmol/liter) in contrast to the changes they observed in visual P300.

G. Summary

Visual P300 and its relationship to diabetes remains relatively unknown. From the small amount of published work, no significant abnormality is evident in patients with either IDDM or NIDDM, although more studies are required to confirm this. Visual P300 during hypoglycemia (arterialized blood glucose, 2.6 mmol/liter), although prolonged both in diabetic and nondiabetic subjects, is affected more in subjects with diabetes. Evidence also exists to suggest that visual P300 is more sensitive to hypoglycemia than auditory P300.

V. Color Vision

A. Historical and technical aspects

In addition to the electrophysiological changes that are associated with vision in diabetes, psychophysical abnormalities also occur. These relate primarily to central or foveal vision and, of these, color vision and contrast sensitivity are relatively noninvasive and simple to perform. As a predominantly macular function, color discrimination may be impaired by any degenerative process affecting the retina (80). In diabetes, abnormalities in color vision were first described in 1953 (81). In common with other aspects of dysfunction in the visual pathway, the underlying mechanism is uncertain and may relate to metabolic derangement in the retina rather than to microvascular disease (82). Various tests are available to assess color vision, and the results can be affected by the presence of lens opacities or color blindness (83). One of the most widely used is the Farnsworth-Munsell 100-Hue Test (84). In a study of young subjects with IDDM, this test was shown to be relatively more sensitive and specific in detecting dysfunction of the visual pathway compared with measurements of both flash and PERG (85).

B. Color vision and diabetes

After initial reports of altered color vision in patients with diabetes (81), a number of experimental studies have been conducted in the past 25 yr to assess this association formally (80, 83, 85–90). With the exception of one study (88), the results all confirm a significant deterioration in color vision (mainly assessed by the 100-Hue Test) in diabetic subjects without retinopathy compared with nondiabetic controls. More specifically, spectral losses of yellow-blue discrimination (tritanopia) have been observed in people with diabetes with varying frequency; 30% (87), 70% (52, 80) and 80% (83). As a congenital finding, tritanopia is very rare but has been reported in several different pathological conditions including diabetes, (52) all of which may be linked by neuronal hypoxia. Tritanopia is distinct from the red-green spectral losses that can be seen in lens changes, particularly opacification, providing further evidence that these reported yellow-blue color defects relate to alterations at the retinal level and not within the lens (80). The frequency of this abnormality has important implications for the interpretation of blood glucose concentrations when reading a visual strip (91,

92). Lombrail *et al.* (87) showed that diabetic patients misread blood glucose strips twice as frequently as nondiabetic controls, prompting the authors to propose that tests of color discrimination should be employed more widely in diabetic patients who perform self-monitoring of blood glucose. Alternatively, diabetic patients should be encouraged to use glucose meters wherever possible to avoid the effect of altered color vision on matching color changes.

C. Type of diabetes

Most studies have been conducted exclusively in patients with IDDM. Several studies have included a small number of subjects with NIDDM (80, 89, 90), but no comparative analyses of the results were performed.

D. Duration of diabetes

Some studies have performed correlational analysis between color vision indices and duration of diabetes with conflicting results. Four groups did not find a significant association (52, 83, 86, 88). By contrast, two studies (80, 93) noted that poorer performance in the 100-Hue Test was associated with longer duration of diabetes. As they included patients both with and without retinopathy, however, this may reflect the fact that those with longer diabetes duration were more likely to have retinopathy that affected their color vision independently (*vide infra*).

E. Glycemic control

Poor glycemic control (as measured by HbA1c) was shown to correlate significantly ($r = 0.24$; $r = 0.3$) with deterioration in color vision in two studies (52, 94). This finding, however, was not replicated in four other studies that examined this association (80, 83, 86, 88). Hardy *et al.* (82) studied the effect of short-term increases in blood glucose (14 mmol/liter) but did not find any changes in color vision compared with the results obtained during euglycemia.

F. Age of subject

Although one study included children within its cohort of subjects (52), no studies have been specifically directed at assessing color vision in children with diabetes. Some studies have included adults with a wide age range (80, 90), and Lakowski *et al.* (80) showed that increasing age was associated with deteriorating color vision in both the diabetic and nondiabetic groups. In their 7-yr prospective study, Aspinall *et al.* (90) reported that, in the subjects under 40 yr of age, diabetes duration was found to be the best predictive indicator of retinopathy development. By contrast, in those over 40, yellow-blue color discrimination was the best single predictive parameter.

G. Retinopathy status

Several studies have examined the association between abnormal color discrimination and diabetic retinopathy (80, 83, 87–90, 93, 95). Lombrail *et al.* (87), although reporting that one-third of their diabetic subjects had significant dyschromatopsia, did not find any difference between those with and without diabetic retinopathy. In a separate study, the same group (95) detected a deterioration in 100-Hue Test scores in subjects with IDDM who had retinopathy but did not find any correlation with early retinopathic changes. Two other groups reported a significant deterioration in performance on color testing in subjects with retinopathy, particularly in the yellow-blue spectral region (80, 90). The degree of retinopathy also appears to be important. Bresnick *et al.* (89) found a positive correlation between color discrimination and extent of retinopathy. Sixty-five percent of those with proliferative changes had abnormal 100-Hue Test results and those with central changes, especially macular edema, were most affected. In a separate study Roy *et al.* (88) also found that the subjects who had PDR performed most poorly.

H. Color vision and hypoglycemia

Lakowski *et al.* (80) made the first report of color changes during hypoglycemia when one of their subjects accidentally experienced an episode of hypoglycemia during one of the study sessions. Although the subject was unaware of any deterioration in vision during the episode, formal color vision examination confirmed a deterioration in performance that corrected on retesting once euglycemia had been restored. Harrad *et al.* (57) conducted the first experimental assessment of color vision during hypoglycemia. Using the 100-Hue Test, they reported a deterioration in performance during acute hypoglycemia both in diabetic and nondiabetic subjects. It should be noted that the degree of hypoglycemia induced by intravenous injection of insulin was variable and often profound (mean venous blood glucose 1.9 ± 0.4 mmol/liter). Any alteration in color vision reported may be due to changes in cognitive function that would affect performance in the 100-Hue Test, which takes time to complete and requires concentration and decision making. In a more recent study, Hardy *et al.* (82) studied the effect of more constant hypoglycemia induced by a glucose clamp method (arterialized blood glucose, 2.5 mmol/liter) in aretinopathic diabetic subjects but did not find any significant changes in 100-Hue Test scores when compared with the results obtained at euglycemia (5.0 mmol/liter).

I. Summary

The assessment of color vision may be more sensitive than ERG in the detection of early visual dysfunction. Specific spectral losses, especially yellow-blue discrimination, are widespread in patients with diabetes, irrespective of the presence of retinopathy and duration of diabetes. The results from subjects with background retinopathy are conflicting, although, as expected, the presence of more advanced retinopathy or maculopathy has a greater effect on color vision. The data for color vision's changes during acute changes in blood glucose (hyper- and hypoglycemia) and its correlation with longer term glycemic control are inconclusive.

VI. Contrast Sensitivity

A. Historical and technical aspects

Contrast sensitivity is defined as a measure of the amount of contrast between light and dark (monochrome or color) required to detect or recognize a visual target (96). This measurement has been shown to provide information about visual function that is not assessed by Snellen acuity (97) or visual field testing and has the advantage of being quick to perform, inexpensive, and relatively free from bias (98). Contrast sensitivity may be measured at various spatial frequencies to detect functional defects in spatially sensitive retinal ganglion cells or in higher visual pathways, both in dynamic and static modes (moving and stationary images). Unfortunately, the variety of measurement procedures, the calibration required, and the equipment used preclude direct comparisons of the results from different studies.

Although both hue discrimination and contrast sensitivity reflect macular function, their exact physiological relationship has not been fully explained. Trick *et al.* (94) directly compared the ability of these two parameters to detect early visual dysfunction in diabetic patients. They found that 37.8% of aretinopathic subjects had evidence of abnormalities on either test, this figure rising to 60% in those with background retinopathy. Contrast sensitivity was abnormal more frequently than color discrimination (measured by the 100-Hue Test), and it appeared to be uncommon for individual subjects to exhibit simultaneous deficits both in contrast sensitivity and color vision. Brinchmann Hansen *et al.* (99) also found that contrast sensitivity correlated more closely to the grade of retinopathy than either color vision or macular recovery (another parameter of psychophysical function).

B. Contrast sensitivity and diabetes

Significant losses of contrast sensitivity have been observed in patients with IDDM who had no evidence of retinopathy when compared with nondiabetic controls (94, 96, 98, 100, 101), particularly in spatial frequencies in the mid to high range (94, 96, 101). Di Leo *et al.* (96) also demonstrated that these changes occur both in dynamic and static modes, the latter appearing to be more sensitive to early changes. By contrast, Sokol and colleagues (97) reported that contrast sensitivity was normal in patients with IDDM who had no retinopathy.

C. Type of diabetes

Some studies have included patients with NIDDM as well as IDDM in their patient groups (94, 97). Sokol *et al.* (97) found significant changes in contrast sensitivity at 22.8 cycles/degree in the NIDDM group whereas the IDDM group results were normal ($P < 0.01$). Trick *et al.* (94), however, did not find any differences between the IDDM and NIDDM patients they studied.

D. Duration of diabetes

IDDM of short duration was shown to be associated with significant contrast sensitivity losses at all but the highest spatial frequencies (96). Two other studies also demonstrated a significant negative correlation between contrast sensitivity and duration of diabetes in IDDM and NIDDM of longer duration (94, 97), although this relationship was not found in a separate study by Buckingham and Young (102).

E. Glycemic control

Two studies have demonstrated a positive correlation between poor glycemic control, as assessed by HbA1c, and deteriorating contrast sensitivity (96, 100). Banford *et al.* (100) found a significant correlation ($r = -0.142$) at 6 and 12 cycles/degree, whereas Di Leo *et al.* (96) reported positive correlations ($r = 0.34-0.51$) at multiple spatial frequencies. By contrast, one study failed to show any significant relationship between contrast sensitivity changes and HbA1c (94).

F. Age of subject

Most of the studies reported in the literature examined contrast sensitivity in adults with diabetes. One study also included children and analyzed their results separately for this group (97). They showed small, but significant, differences in contrast sensitivity scores between children with diabetes and nondiabetic controls at two spatial frequencies. This contrasts with their findings in adults with IDDM who did not differ from their nondiabetic counterparts in tests of contrast sensitivity.

G. Retinopathy status

The evidence regarding the association between abnormal contrast sensitivity and the presence of retinopathy is conflicting. Ghafour *et al.* (101) demonstrated a significant increase in the contrast sensitivity threshold, which was most marked in a diabetic group who had PDR, but was also elevated significantly in the diabetic group with background retinopathy when compared with patients with no retinopathy. Sokol *et al.* (97) also reported abnormal contrast sensitivity at all spatial frequencies in a group of NIDDM patients with background retinopathy. Howes *et al.* (103) and Hyvarinen *et al.* (104) both reported changes in contrast sensitivity that related to the degree of retinopathy. Brinchmann Hansen and colleagues also found an association between contrast sensitivity and grade of diabetic retinopathy, but only at 6 cycles/degree (99). By contrast, Collier *et al.* (105) and Banford *et al.* (100), in separate studies, did not find any significant difference in the performances of patients with IDDM and retinopathy compared with those who had no retinopathy, although the numbers involved in one study (100) were very small (only 8.3% of patients had retinopathy). Bangstad *et al.* (106) used a novel approach to assess the relationship between contrast sensitivity changes and microvascular diabetic complications by studying subjects who had established microalbuminuria and comparing their performance in tests of contrast sensitivity to diabetic controls who did not have microalbuminuria. They showed that, independent of background retinopathy, contrast sensitivity was impaired in the subjects with microalbuminuria.

H. Contrast sensitivity and hypoglycemia

Di Leo and colleagues (96) have postulated that recurrent episodes of minor hypoglycemia may be responsible for the underlying physiological changes to the optic nerve that result in the nonselective loss of contrast sensitivity that this group has detected in early IDDM. Hypoglycemia has been shown to impair contrast sensitivity in nondiabetic subjects (58), and a recent study (107) in diabetic subjects demonstrated a trend toward impaired performance in this test, although this was less pronounced than the nondiabetic subjects, under similar test conditions. Hyperglycemia has also been shown to affect contrast sensitivity significantly in people with IDDM who do not have retinopathy while visual acuity remained unchanged (108).

I. Summary

Contrast sensitivity testing, in common with color vision (another test of psychophysical function), demonstrates significant changes in diabetic subjects compared with nondiabetic controls, and there is some evidence for a relationship with grade of retinopathy. Changes in contrast sensitivity have been demonstrated in children and adults with diabetes of short duration, and some evidence exists for a correlation with poor glycemic control, although prospective studies are required to assess this relationship over a longer time period. Although both color vision and contrast sensitivity demonstrate similar patterns, studies that directly compare the two tests suggest that measurement of contrast sensitivity is the more sensitive and specific.

VII. Conclusions

It is evident that diabetes has an effect on electrophysiological and psychophysical aspects of vision. Retinopathy, as an important complication of diabetes, clearly has a role in promoting these abnormalities, but changes in visual function in diabetes occur before any structural abnormalities can be detected by ophthalmoscopy or even by fluorescein angiography. Visual abnormalities in diabetes should therefore be viewed in the context of visual function as a sensory *system*, beginning at the anterior chamber of the eye and involving the retina, optic nerve, central pathways, occipital cortex, and ultimately requiring higher cerebral function to perceive and respond to the stimulus. The techniques described enable assessment of this system at various stages and have an important place in clinical research, expanding our knowledge of electrophysiological and neuroretinal function within the wider field of the effect of diabetes on the central nervous system, an area that has received much less attention than the pathophysiology of the peripheral nervous system. It is necessary to consider how such techniques and the information they provide can be applied to current clinical practice to improve our approach to patient care.

ERG, as an index of retinal electrical activity, is able to detect abnormalities at the retinal level before overt pathology is visible. Changes both in flash and PERG have been clearly demonstrated in patients with diabetes, although the relative merits of each test are still unclear. The association between retinopathy and ERG changes is an important one. One of the few long-term prospective studies in this field (17, 29) has shown the potential predictive use of this technique in identifying those patients who are at greatest risk of developing retinopathy in the future. Although present technical limitations make this a test that is available only through specialist-referral centers, it provides an important research tool, the use of which may be extended eventually to a wider number of diabetic patients in the clinical setting to identify those who require the most intensive ophthalmological follow-up.

P100 assesses the visual pathway from retina to visual cortex and, as such, provides important information about neural pathways within the brain. There is strong evidence of widespread P100 abnormalities both in IDDM and NIDDM, indicating that this may be a useful test to detect early visual dysfunction as part of the syndrome of 'diabetic encephalopathy.' The lack of correlation with retinopathy suggests that this parameter is most useful in assessing the postretinal visual pathway and providing information about previously unsuspected visual dysfunction. Although short-term improvements in glycemic control may partially reverse these changes, the evidence for any correlation with HbA1c is very limited. The DCCT (32) demonstrated that improvement in glycemic control, as measured by HbAlc, correlated with reduced rates of diabetic retinopathy. Such a relationship, however, has not been irrefutably shown in the small number of electrophysiological studies that assess any relationship between longer term glycemic control and changes in vision. Although this raises the question of the significance of any changes demonstrated in this area to clinicians working in diabetes, the fact that electrophysiological changes have been shown to occur early in the disease process provides evidence for aspects of visual dysfunction distinct from retinopathy whose clinical significance is yet to be fully demonstrated. Longer term prospective studies may also show the predictive value of these tests in assessing patients most at risk of developing retinopathy, as has been shown in the field of ERG (17, 29). The conflict in data concerning any association with changes in peripheral nerve conduction requires further research.

P300, as a marker of cognitive function in vision and other sensory modalities, provides useful information as it links the visual pathway to higher brain centers. Few studies are currently available relating to visual P300, and most of the research in this area relates to the changes induced by short-term hypoglycemia. More research is required to evaluate the wider implications for visual cognition, especially in its relationship to P100.

Both P100 and P300 require a degree of technical expertise to obtain reliable and reproducible results. Like ERG, therefore, both tests are likely to remain restricted to specialist centers, although they provide an invaluable tool in assessing brain structures that are inaccessible by other techniques. With increasing interest in the effects of diabetes on the brain, they complement other techniques to enhance our understanding of the central nervous system.

Practicality and patient acceptability are important aspects of any widely used screening test. The psychophysical tests of both contrast sensitivity and color vision meet these cri-

teria and have the potential to be of use in primary care settings as well as the hospital diabetes clinic. There is good evidence that abnormalities are present in diabetic patients without overt retinopathy. These tests, which are simple and quick to perform, could complement the existing screening tests for retinopathy, providing additional information about visual function, especially its change over time. Any role these tests have to play in routine screening for early visual dysfunction remains to be evaluated, but an easily performed test of clinical value with high sensitivity and specificity is obviously desirable.

Diabetic retinopathy, although the major cause of visual loss in the diabetic population, is not the sole aspect of visual dysfunction in this group, and it is important to consider other aspects of visual dysfunction occurring in people with diabetes that remain undetected by present methods of routine clinical assessment.

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